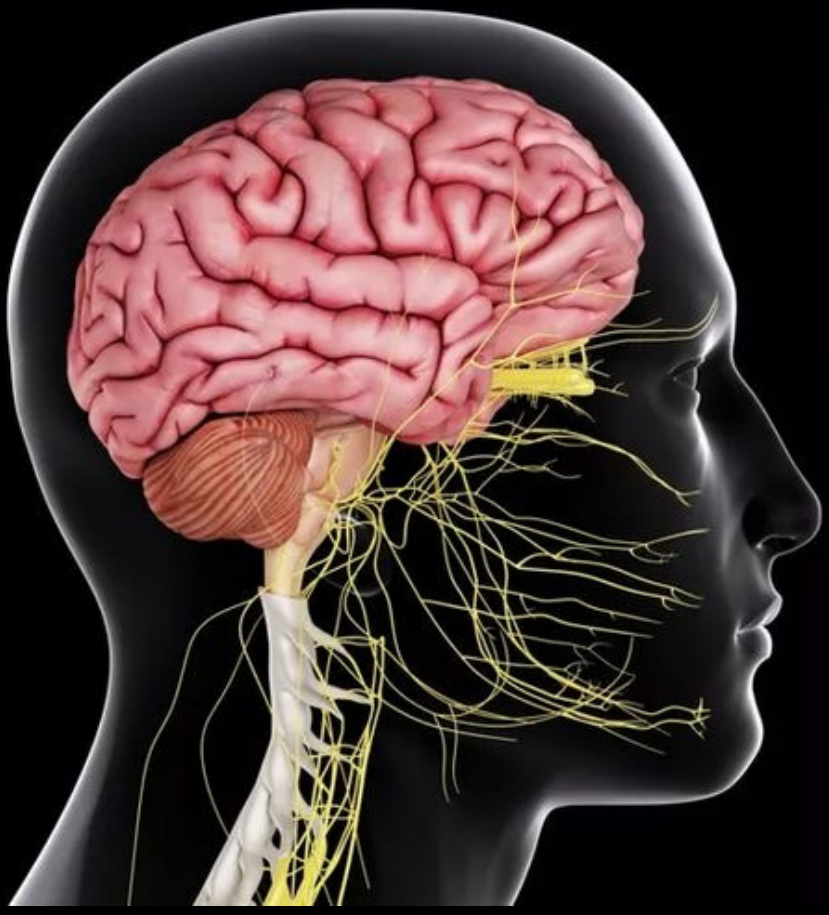
النادي الطبي

CENTRAL NERVOUS SYSTEM



SUBJECT : Pharmacology

LEC NO. : 6

DONE BY : Feras Atieh

وقل رب زدني علماً

Anxiolytics and Hypnotics

Pharmacology and Toxicology

Central Nervous System Module

Third Year Medical Students

Tareq Saleh

Faculty of Medicine

The Hashemite University

هلأ احنا كلنا بننصاب ب anxiety بس هاي ال anxiety ما بتحتاج علاج ولا دواء وبتكون جزء من حياتنا اليومية زي واحد إجاله خبر حزين،واحد عليه امتحان وهكذا بس ال Anxiety disorders الهم مواصفات criteria for the diagnosis described state of chronic anxiety وغالبا همة بكونو

Anxiety

- Anxiety is an unpleasant state of tension, apprehension or uneasiness (a fear that arises from either a known or an unknown source). **Anxiety usually is associated with physicsl symptoms**
- Physical symptoms of anxiety are a result of sympathetic activation: tachycardia, sweating, trembling and palpitations).
- Anxiety disorders include: Generalized anxiety disorder, panic disorder, obsessive compulsive disorder, phobias, etc.

Tareq Saleh ©

Wolters Kluwer

Anxiolytics: Classes of Drugs

BENZODIAZEPINES

Alprazolam XANAX
Chlordiazepoxide LIBRIUM
Clonazepam KLONOPIN
Clorazepate TRANXENE
Diazepam VALIUM, DIASTAT
Estazolam
Flurazepam DALMANE
Lorazepam ATIVAN
Midazolam VERSED
Oxazepam
Quazepam DORAL
Temazepam RESTORIL
Triazolam HALCION

BENZODIAZEPINE ANTAGONIST

Flumazenil ROMAZICON

OTHER ANXIOLYTIC DRUGS

Antidepressants VARIOUS (SEE CHAPTER 10)
Buspirone BUSPAR

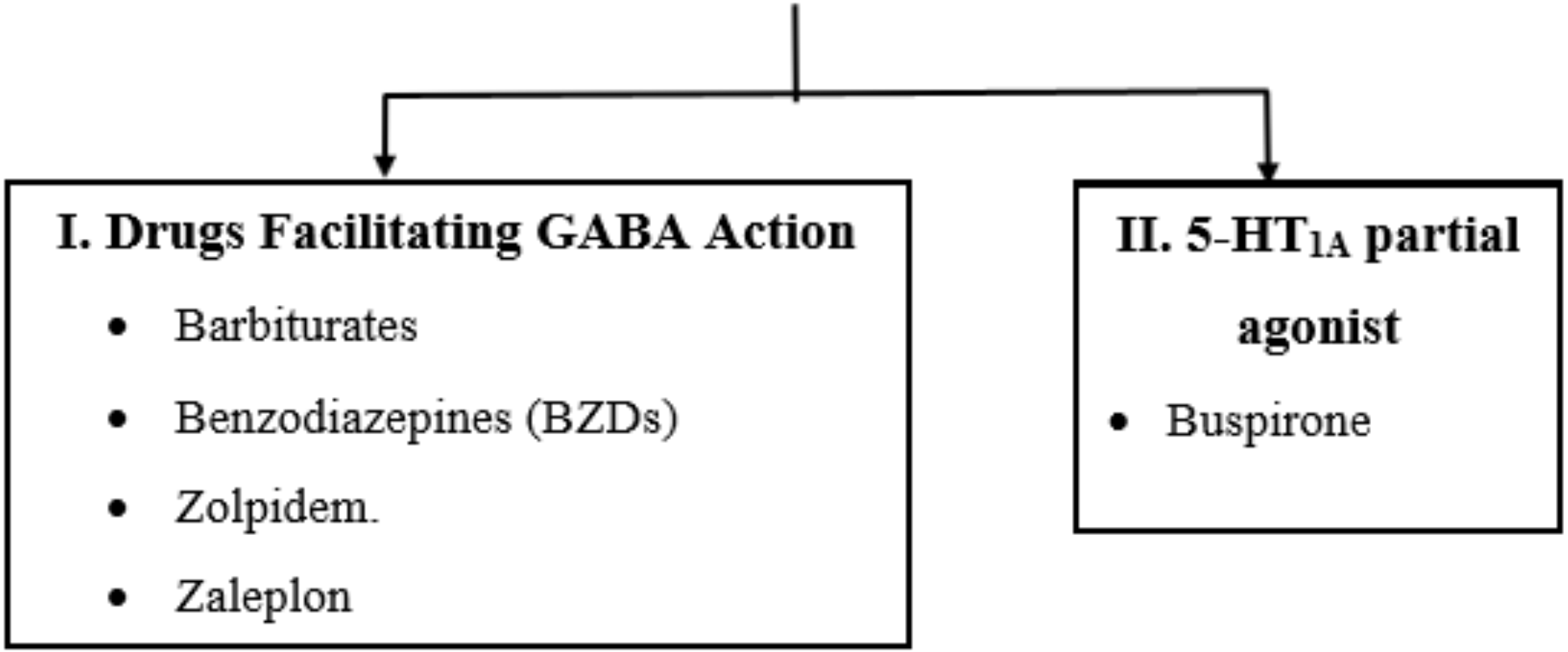
BARBITURATES

Amobarbital AMYTAL
Pentobarbital NEMBUTAL
Phenobarbital LUMINAL SODIUM
Secobarbital SECONAL
Thiopental PENTOTHAL

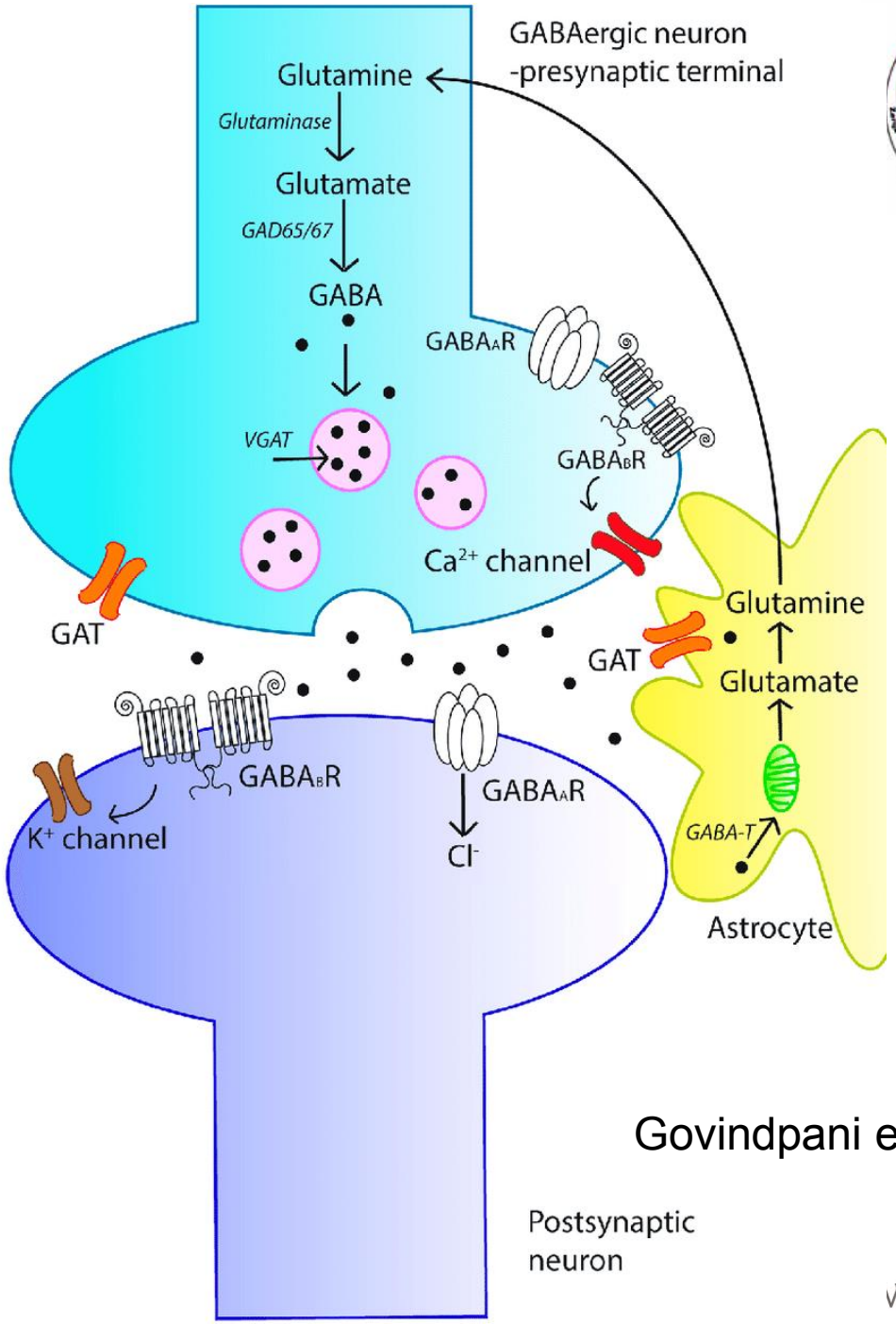
OTHER HYPNOTIC AGENTS

Antihistamines VARIOUS (SEE CHAPTER 30)
Doxepin SILENOR
Eszopiclone LUNESTA
Ramelteon ROZEREM
Zaleplon SONATA
Zolpidem AMBIEN, INTERMEZZO, ZOLPIMIST

Classification According to Mechanism of Action



The GABAergic Synapse



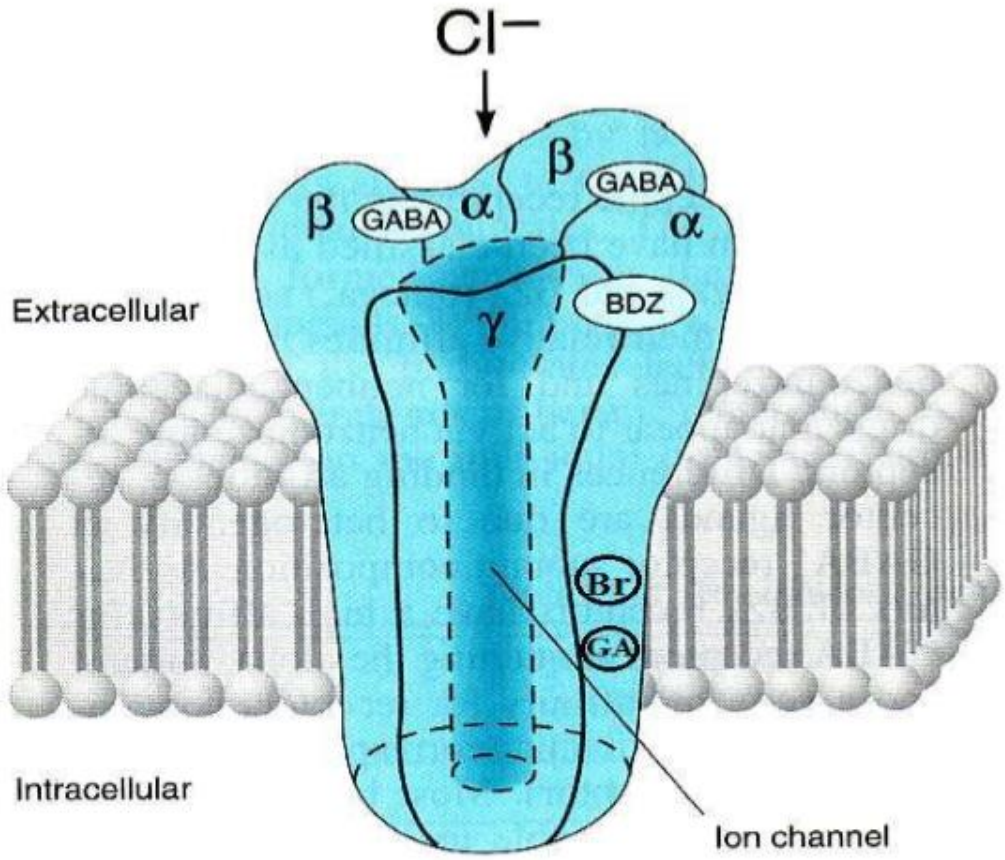
Govindpani et al, 2017

GABA Receptors

- Receptors for the inhibitory neurotransmitter γ-aminobutyric acid (GABA).
- Two main receptors types:

❑**$GABA_A$ receptors**: ligand-gated ion channels (*ionotropic*) chloride بدخل

❑**$GABA_B$ receptors**: G-protein-coupled receptors (*metabotropic*)

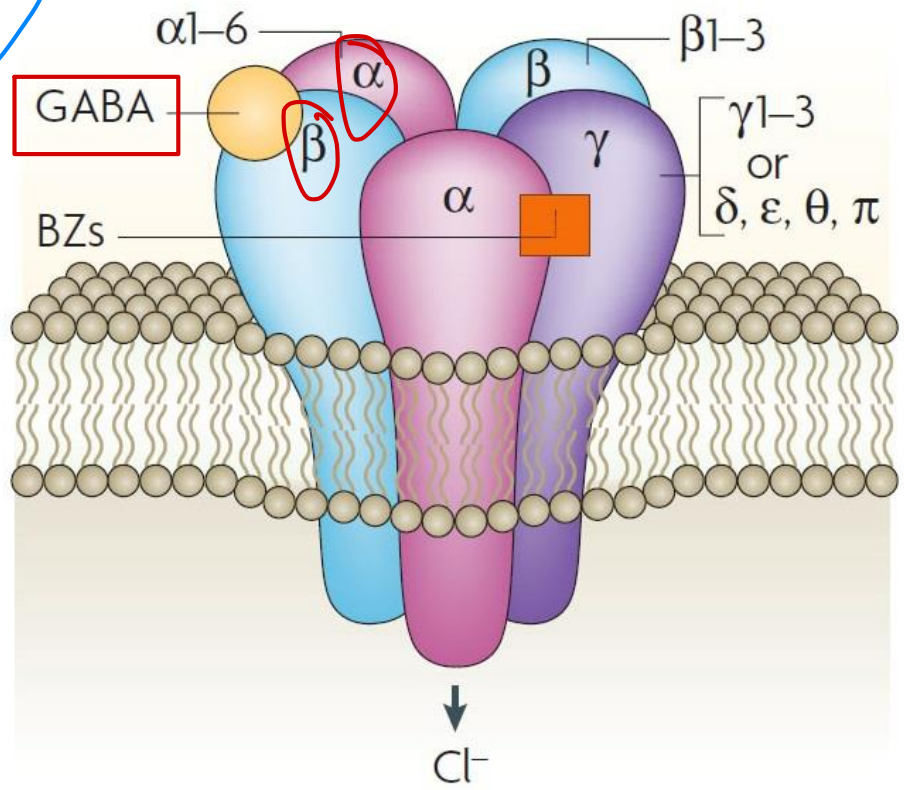


$GABA_A$ Receptor

يعني بتكون من 5 subunits (2a,2B,1Y)

Most commom

- *pentamer* formed of 3 different types of subunits (two α, two β and one γ) surrounding a Cl^- ion channel.
- The GABA binding site is at the interface between α and β subunits.
- Binding of 2 GABA molecules triggers the opening Of the central ion channel allowing for chloride influx.
- The influx of chloride → hyperpolarization → decreases action potentials (neurotransmission).



١-هلأ ال 5 subunits اللي بيعملو ال GabA,A receptor الهم أنواع يا بكونو ألفا يا بكونو بيتا يا بكونو جاما وبرضه كل وحدة منهم الها أنواع يعني في عنا

- **6 different types of alpha**
- **3 different type of beta**
- **3 different type of gamma**

بيختلفو بال structure

٢-فإحنا هلأ ممكن نعمل **different combinations of GABA,A Receptor** يعني **GABA,A Receptor** اللي فيو alpha 1 subunit شوي بيختلف عن GABA,A Receptor اللي فيو alpha 2 subunit وشوي بأثر بيختلف عال function

٣-احنا بنحتاج **2 molecules of GABA** بيربطو على receptor binding side موجود بين الألفا والبيتا حتى تفتح ال Central ion channel ويدخل ال chloride

يعني بإختصار احنا عنا **GABA,A Receptor** بتكون من **Subunits 2alpha,2beta,2 gamma** ومكان ارتباط ال **GABA** بكون بين الألفا والبيتا

Benzodiazepines

Not Agonist

The agonist binds at the same binding site results in activation

different site but result in the activation بربطو على

Benzodiazepines

يعني هذول الأدوية بتربط على نفس ال receptor بس different binding site بين الألفا والجاما بدل البيتا

Mechanism of action:

- Benzodiazepines are allosteric modulators of $GABA_A$ receptors.
- They bind to distinct, high-affinity site from the GABA-binding site located at the interface between the α and γ subunits.
- These binding sites are labeled as benzodiazepine (BZ) receptors.
- CNS BZ receptors:

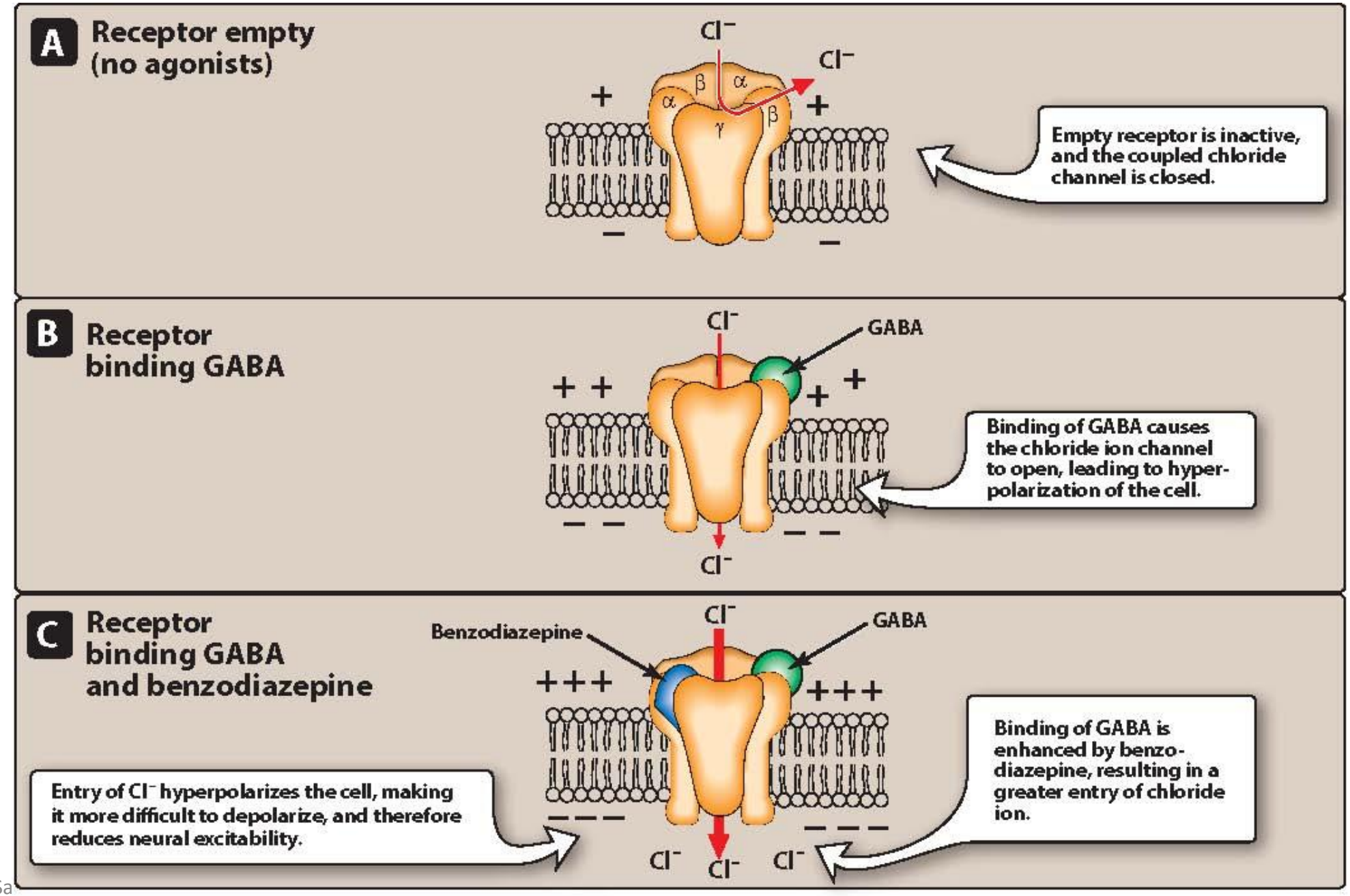
❑ **BZ_1** includes α_1 subunits (mediate sedation, hypnosis, amnesia and antiepileptic effects)

❑ **BZ_2** includes α_2 subunits (anxiolytic and muscle relaxant effects)

Benzodiazepines

Mechanism of action:

- Binding of benzodiazepines to the BZ receptors on the $GABA_A$ receptor complex → **increases affinity** of GABA to bind to its receptors. This **increases the frequency of opening** of Cl^- channel → facilitating the inhibitory effects of GABA.



Benzodiazepines

Actions: Suppress CNS functions

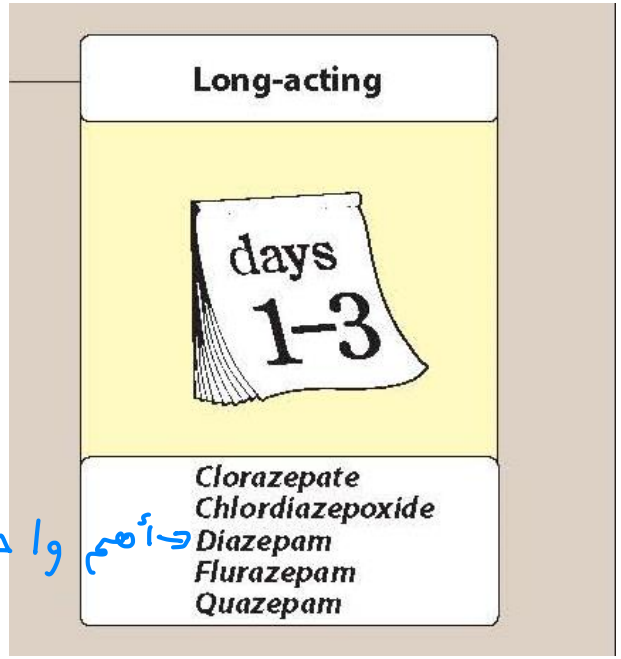
- **Reduction of anxiety:** through α_2 subunit containing $GABA_A$ receptors.
- **Sedative/hypnotic:** through α_1 subunit containing $GABA_A$ receptors. (Artificially induced sleep)
- **Anterograde amnesia:** through α_1 subunit containing $GABA_A$ receptors.
- **Anticonvulsant:** through α_1 subunit containing $GABA_A$ receptors.
- **Muscle relaxant:** through α_2 subunit containing $GABA_A$ receptors.

هلأ بناءًا على Actions تاعونهم بقدر أستعملهم ك theraputic uses مثل

1-anti seizure effect
2-treat anxiety
3-relax muscles with patients with severe muscle rigidity
4-insomnia

Benzodiazepines: Duration of Action

هلأ هذول الأدوية not first line treatment لأي استعمال من الاستعمالات اللي حكيناها فوق لإنهم highly dangerous+dependence can happen really fast



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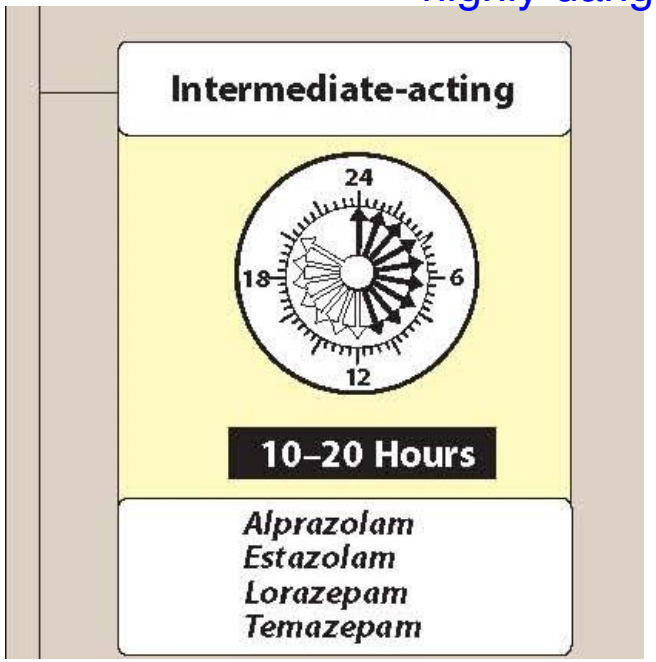
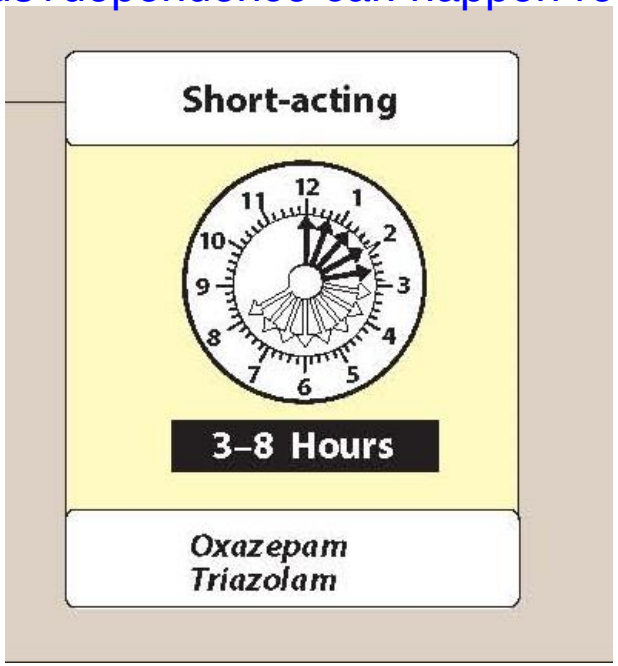




Duration of action duration of action بال بس بيختلفو effect ال كلهم نفس

- determine therapeutic uses **(half-life is very important)**
- **with some benzodiazepines, the clinical duration of action does NOT correlate with the actual half-life** Becuase they are stored in fat tissues (very lipid soluble)

half life is not equal to the actual effect ال انه يخدعك فممكن

Benzodiazepines

1-shouldn't be 1st line for anxiety

2-period of use shouldn't be longer than 2 weeks

Therapeutic uses:

- **Anxiety disorders:**

  - Panic disorder, GAD, OCD, social anxiety disorder, phobias.
  - Anxiety related to depression or schizophrenia.
  - **ONLY** for severe anxiety (NOT for the stress of everyday life).
  - Longer-acting drugs are preferred: **lora**-; **clona**-; and **diazepam**.
  - **Tolerance:** anxiolytic effects < sedative/hypnotic.

Benzodiazepines

Therapeutic uses:

- **Sleep disorders (insomnia)**

❑ Decrease latency to sleep onset AND Increase stage II of non-rapid eye movement (REM) sleep.

❑ commonly used drugs:

1. **Temazepam**: intermediate-acting – given 1-2 hours before bedtime – Best for frequent awakening.
2. **Triazolam**: short-acting – best for inability to go/stay asleep – Rebound insomnia

(using long-acting like flurazepam may result in excessive daytime sedation)

ما بنستخدم long acting لإنه حنخليه يسطل زيادة عن اللزوم ثاني يوم

Benzodiazepines

Therapeutic uses:

- **Amnesia**

❑used as an adjunct to anesthesia: to relief unpleasant, surgery-induced anxiety

❑**midazolam** is often used for this purpose

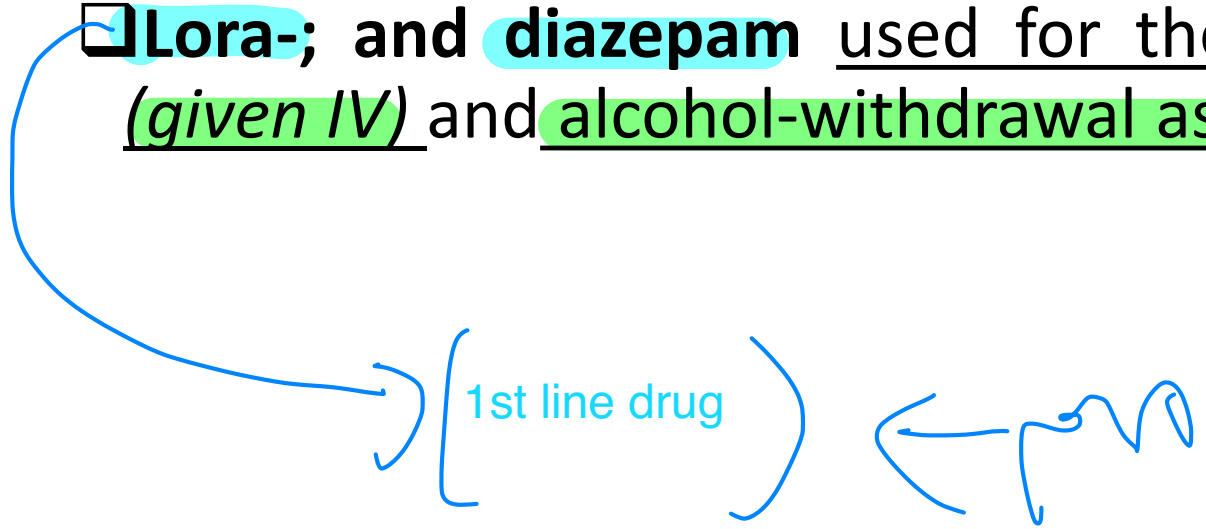
Benzodiazepines

Therapeutic uses:

- **Seizures**

❑**Clonazepam** used as adjunctive therapy for certain types of seizures.

❑**Lora-; and diazepam** used for the treatment of *status epilepticus (given IV)* and alcohol-withdrawal associated seizures.



Benzodiazepines

Therapeutic uses:

- **Muscular disorders**

❑used for skeletal muscle spasms

❑used for spasticity associated with multiple sclerosis and cerebral palsy

Benzodiazepines

Pharmacokinetics

- **Absorption**

  - highly lipophilic

CNS distribution? Fat? Pregnancy?

- **Metabolism**

- ❑ metabolized by hepatic microsomal system
- ❑ mostly the metabolites are also active
- ❑ excreted in the urine

لإنه البيبي بكون dependant أصلا اذا كانت الأم chronic abuser زي ال opioids

Severe withdrawel to fetus because it cross the placental barrier

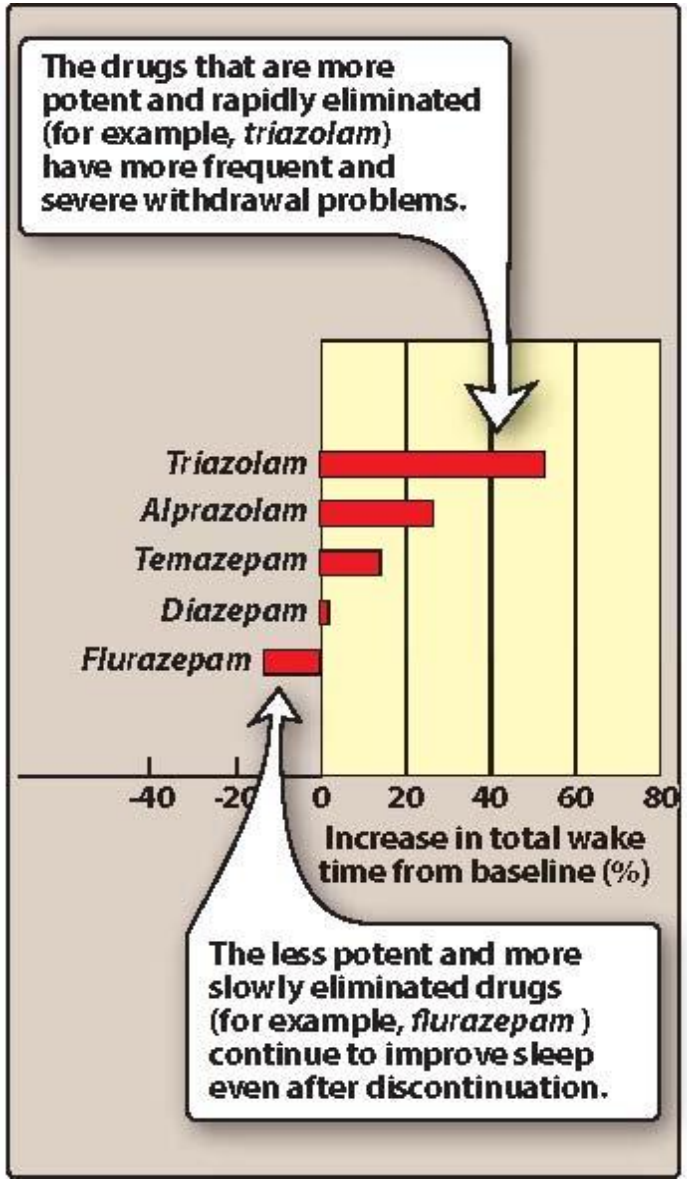
Benzodiazepines

Dependence

- Psychological and physical dependence can develop rapidly
- Used for short periods of time
- Abrupt discontinuation → WITHDRAWAL: لازم بالتدريج

 -confusion, anxiety, agitation, rebound insomnia, tension and seizures.

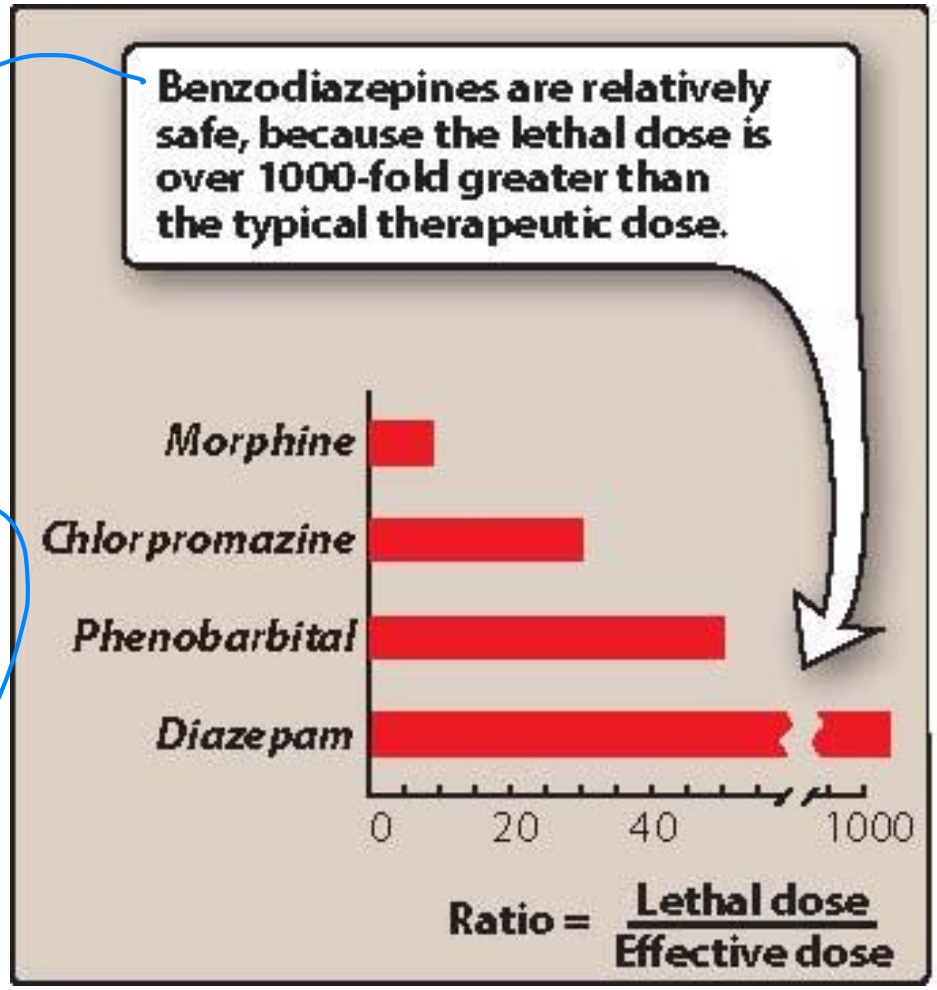
 -withdrawal happens more with short-acting



Benzodiazepines

Adverse effects

- Drowsiness and sedation
  - Driving
  - Cognitive impairment
- Combination with other sedatives can be dangerous:
  - Alcohol, barbiturates, anesthetics, …
- Anterograde amnesia
  - Impaired ability to learn new information.



Benzodiazepine Antagonist: antidote

- **Flumazenil**
  - GABA receptor antagonist
  - used for benzodiazepine toxicity/overdose
  - IV only
  - rapid onset, short duration of action
  - may precipitate withdrawal in dependent patients

Other anxiolytics: antidepressants

- Remember: many antidepressants are used to treat anxiety.
- **SSRIs** (escitalopram, paroxetine) and **SNRIs** (duloxetine, venlafaxine) are FIRST LINE to treat anxiety.
- Often used with a benzodiazepine initially (first 4-6 weeks)

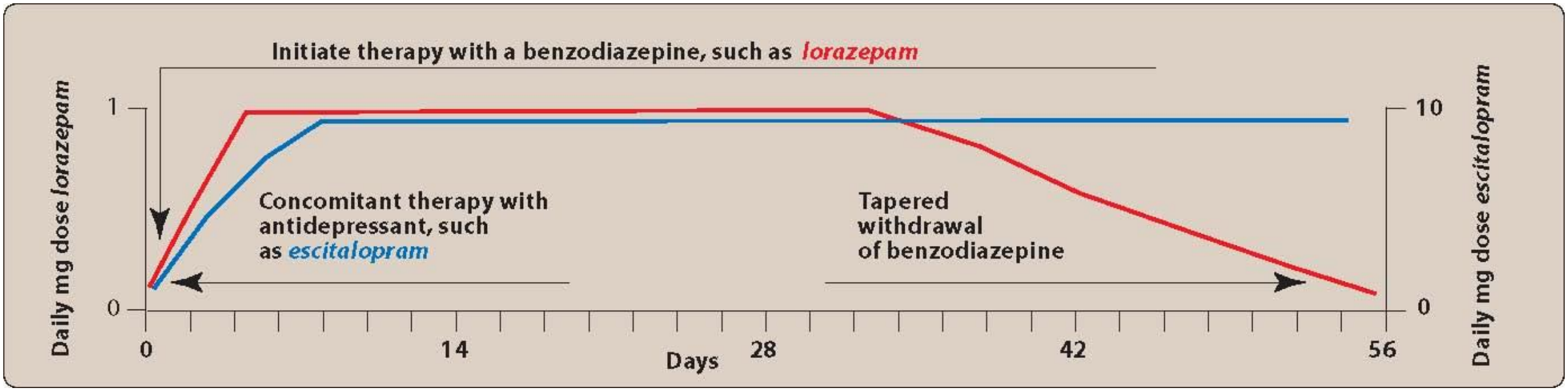
In combination with SSRI and SNRI

ليش ما بستعملهم لحالهم؟

لإنهم بقعدو فترة طويلة تيبلشو تأثير

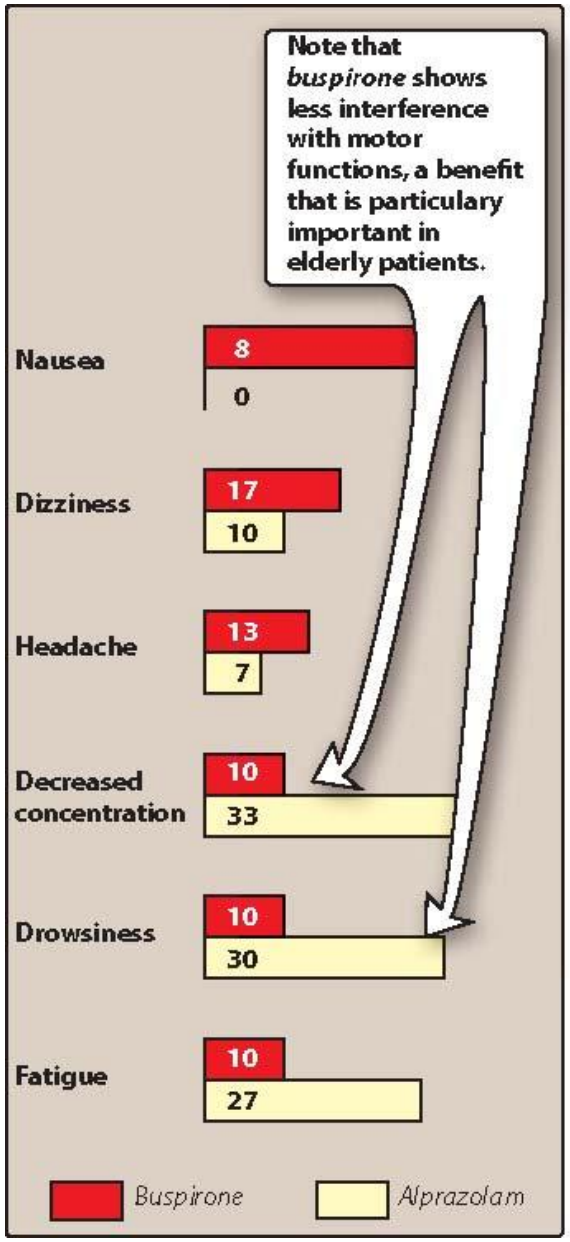
بعدين بعمله gradual discontinuation بكون وقتها ال SSRI اشتغل

Other anxiolytics: Antidepressants



Other anxiolytics: Buspirone

- Useful for the chronic treatment of generalized anxiety disorder.
- Ineffective for short-term "on demand" "as needed" treatment of acute anxiety: slow onset of action.
- Effect mediated by 5-HT1A receptors.
- No anti-seizure or muscle relaxant properties
- No dependence Great alternative for Benzodiazepines



Barbiturates

Barbiturates

Overview:

- Old
- Largely replaced by benzodiazepines as sedative/hypnotics

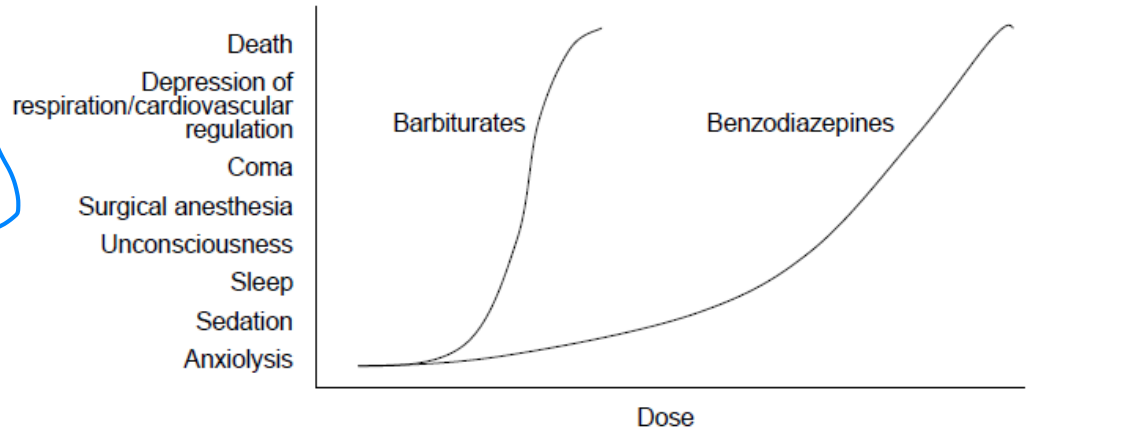
❑ Induce tolerance/dependence/withdrawal/lethal overdose >>>> benzodiazepines

- Some still in use but the majority are not

- example: thiopental is a short-acting barbiturate have been used to induce anesthesia.

Benzodiazepines أسوأ من Barbiturates

Dose-dependent effects of classic sedative-hypnotics



Barbiturates

Mechanism of action:

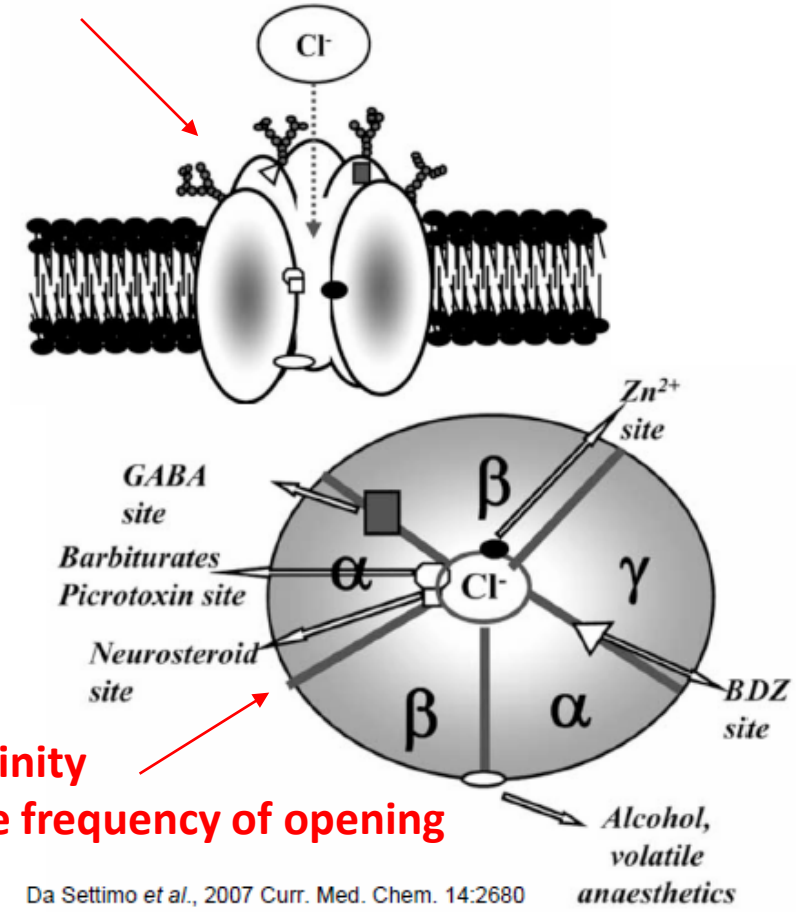
- **Site of action:** $GABA_A$ receptors.
- **Binding site:** different from benzodiazepines

❑ Barbiturates potentiate GABA action on chloride entry by **prolonging the duration** of Cl channel opening.

Barbiturates vs benzodiazepines

The γ-aminobutyric acid ($GABA_A$) receptor

prolonging the duration



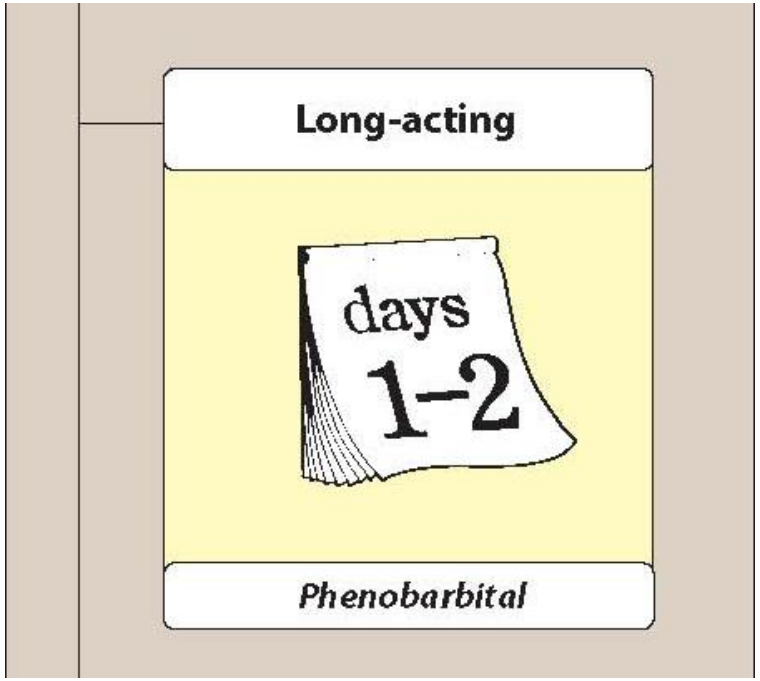
increasing affinity
increasing the frequency of opening

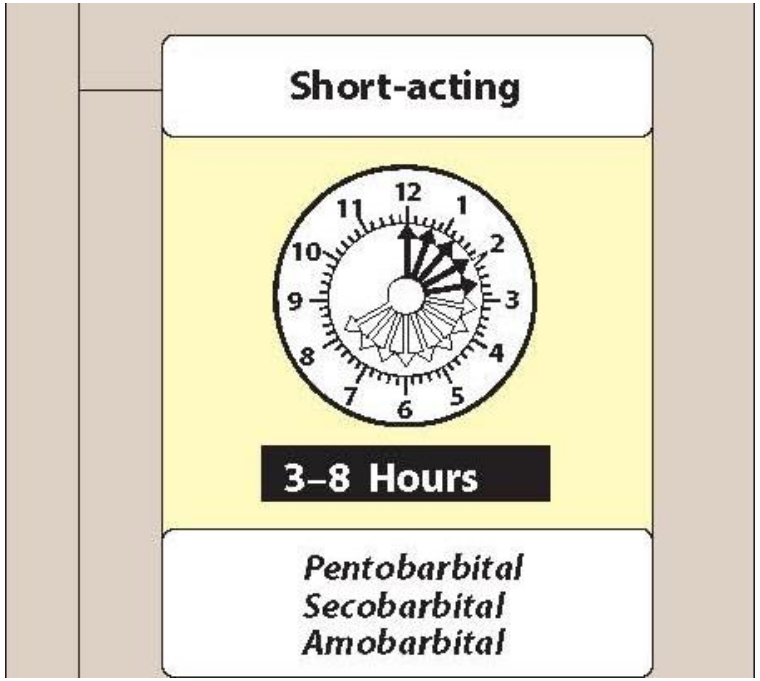
Da Settimo *et al.*, 2007 Curr. Med. Chem. 14:2680

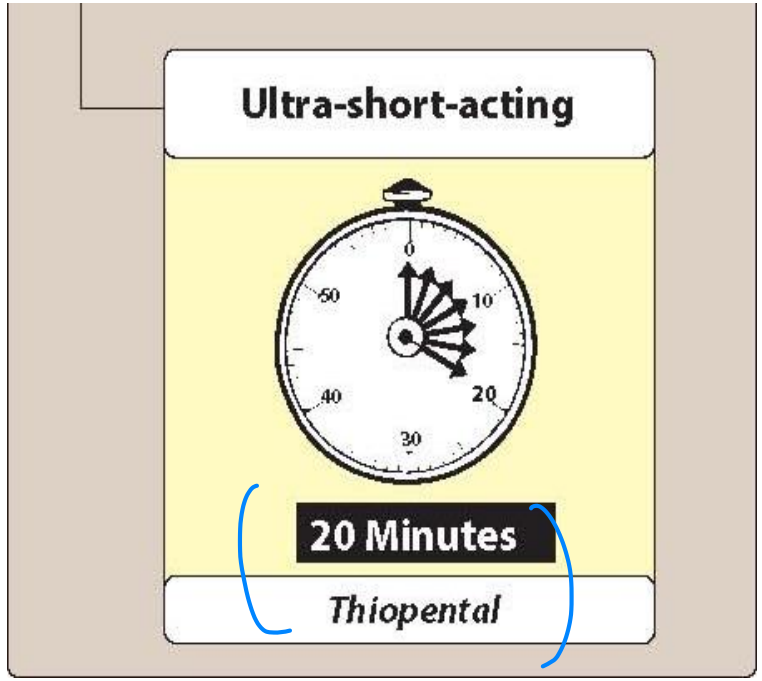
Barbiturates bind to site in ion channel, increasing Cl^- channel open time. Can activate channel at high concentrations.

Benzodiazepines increases affinity of GABA binding site for its ligand. In the absence of GABA, benzodiazepines have no detectable effect on receptor function.

Barbiturates







Barbiturates

Actions:

1- **CNS depression:**

- low doses → sedation
- High doses → hypnosis >>> anesthesia
- Higher doses → coma and DEATH!

2- **Respiratory depression**

Barbiturates

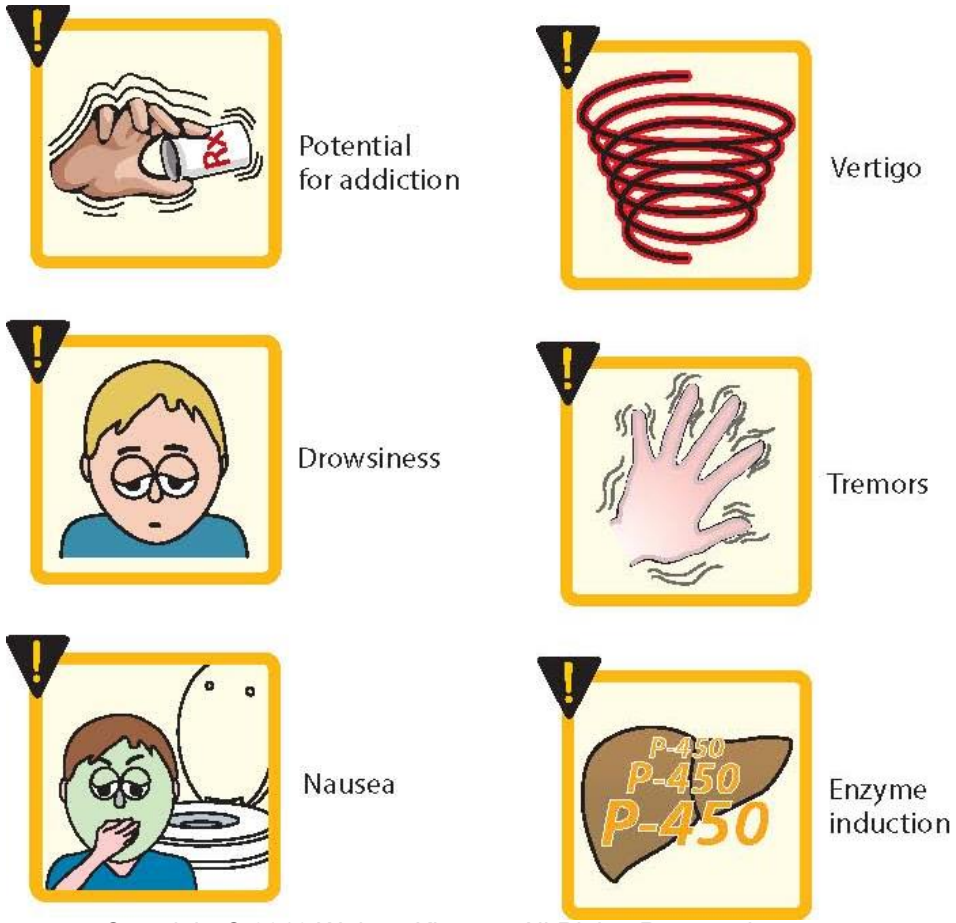
Therapeutic uses:

1. **Anesthesia:** e.g., thiopental for induction of anesthesia (not anymore).
2. **Anticonvulsant:** e.g., phenobarbital for refractory seizures.
3. **Sedative/hypnotic:** for insomnia (no longer accepted)

Barbiturates

Adverse effects:

Barbiturates are contraindicated in patients with acute intermittent porphyria



severe

Withdrawal can result in death

Overdose can result in death

Other Hypnotics: Zolpidem

Alternative for benzodiazepines

- Not a benzodiazepine, but the same mechanism of action (on BZ_1)
- short half-life (2-3 hrs), rabid onset of action.
- Most commonly prescribed drug for insomnia in the US.
- Decrease sleep latency, no effect on sleep.
- Adverse effect: impaired performance in the morning, driving, and dependence.benzodiazepines بس أقل من dependance ممكن يعمل

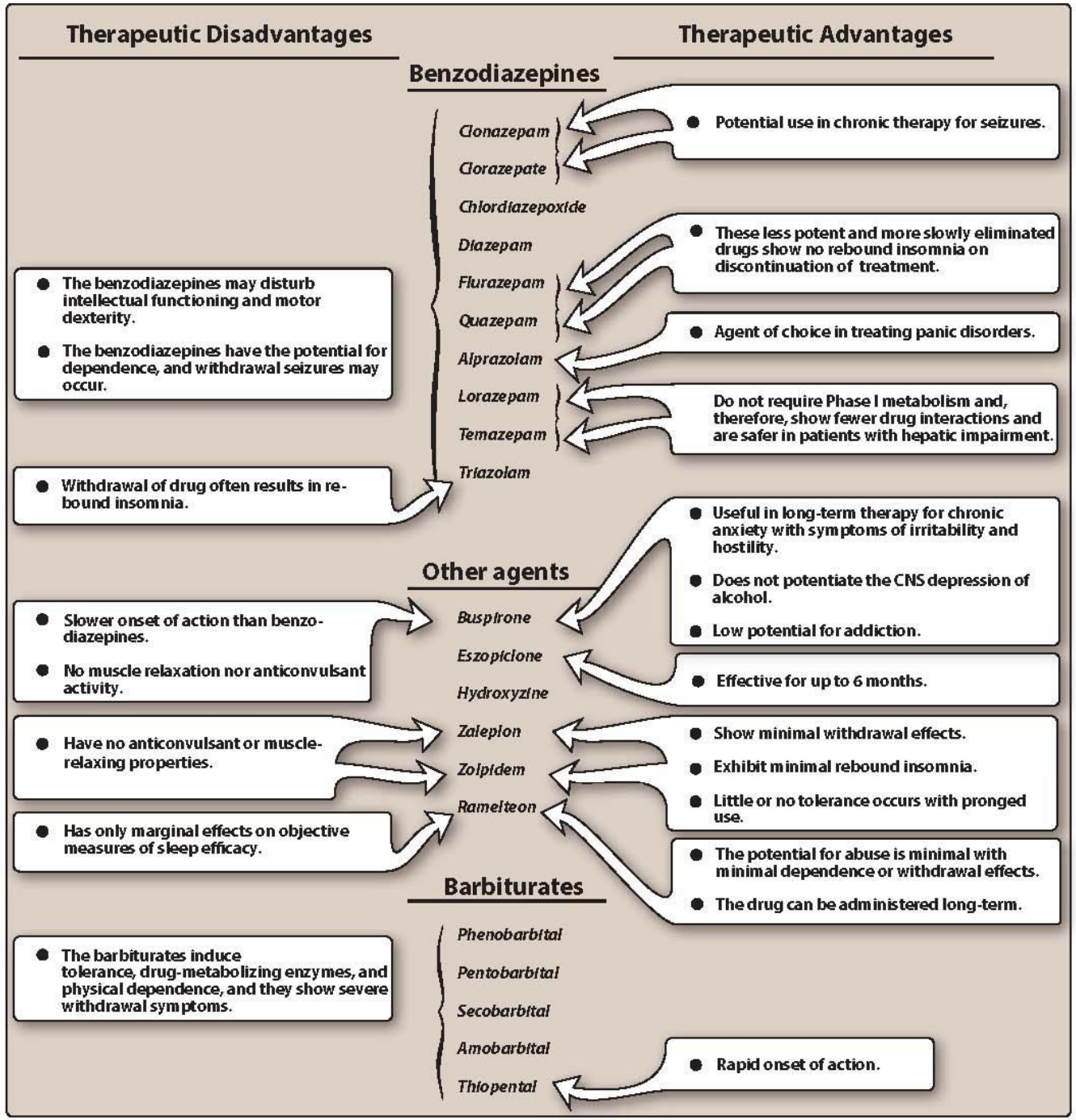
Other Hypnotics: Ramelteon

أحسن من اللي قبليه

- Selective agonist: melatonin receptors 1 and 2
- Indicated for the treatment of insomnia (decreases sleep latency)
- No abuse potential/dependence/withdrawal

Other Hypnotics: Over-The-Counter

- **Antihistamines:**
  - Insomnia (mild).
  - Diphenhydramine.
  - Chlorphenamine (Allerfin).



Summary of Clinical Uses

- Benzodiazepines are indicated only in severe anxiety or insomnia.
- Drug therapy should be started with a small oral dose for a limited period (less than 3 weeks for insomnia) to avoid drug abuse and dependence
- Gradual termination of therapy should be done to avoid withdrawal.
- *Longer-acting* drugs are preferred as *anxiolytics* …*shorter-acting* as *hypnotics*.
- Most benzodiazepines are metabolized in liver → dose adjustment is required in liver cirrhosis to avoid accumulation to toxic levels specially of long acting agents and those metabolized to active metabolites such as diazepam.